REMARKS

Claims 1-30 are pending in the application. Among them, claims 2-4, 21-23, 25-27, and 30 are withdrawn from consideration as being drawn to non-elected inventions. Applicants will cancel these claims upon indication of allowable subject matter. Claims 1, 5-20, 24, 28 and 29 are currently under consideration.

The Examiner has also acknowledged that the amendments filed on Oct. 15, 2002 (Paper No. 16) have been entered in full.

The Examiner indicates that the Abstract may have been separated from the file, and have requested Applicants to submit a copy of the Abstract. Applicants hereby submit a copy of the Abstract page (page 94 of the specification as originally filed) to comply with this requirement.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim rejections under 35 U.S.C. 112, first paragraph

Claims 1, 5-20, 24, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such as way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action alleges that the specification does not contain an enabling disclosure for several reasons as elaborated below.

As a general matter, the test for enablement is whether one of skill in the art could practice the claimed invention without undue experimentation (MPEP 2164.01, also see *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404, Fed. Cir. 1988). However, it is well-settled that "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v.*

Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)." (MPEP 2164.05(a)).

The Office Action asserts that the specification does not teach how to implant a preparation of myogenic precursor cells into a mammal and treat said myogenic precursor cells with an amount of a morphogen sufficient to promote proliferation or differentiation of said myogenic precursor cells into functional myocardium.

Applicants submit that the instant specification teaches in section C, titled "Implantation of Myogenic Precursor Cells at a Myocardial Site" (page 18) how to implant myogenic precursor cells. For example, the specification teaches on page 19 that "...a solution of myogenic precursor cells and a morphogen, morphogen inducer, agonist of a morphogen receptor, or small molecule morphogenic activator, may be implanted at a site of myocardial infarction in essentially the following manner." The same paragraph recites surgical implantation or direct injection as merely two possible means of introducing said solution of myogenic precursor cells and morphogens. Other sections of the specification also teaches the formulation of morphogens suitable for use in the claimed invention (section E starting from page 39), morphogens with enhanced solubility in solution, which is suitable for systemic administration (page 40 and the examples), proper dosages of the morphogens (page 43, 1st full paragraph), and routes for morphogen administration (pages 40-42, systemic, local, topical, or oral administration, etc.). Therefore, the instant specification describes in detail how to implant a preparation of myogenic precursor cells into a mammalian subject, and various means of treating said precursor cells for differentiation into functional myocardium. Furthermore, Fields (WO 95/14079), cited as prior art in the last Office Action (Paper No. 12) confirms that direct injection can be used to introduce various precursor cells directly into the heart of experimental animals (see Examples in Fields).

In addition, it is respectfully submitted that those skilled in the art are well equipped with routine techniques for accessing a heart in vivo. For example, epinephrine is routinely applied to and into the heart via direct myocardial hypodermic injection. Angioplasty is routinely accomplished via percutaneous entry through remote vasculature. Minimally invasive bypass (MIB) techniques, e.g., a thorascopic intercostal approach, are well known for accessing the heart during surgery, e.g., valve replacement, bypass operations. Open heart surgery is another

routine procedure utilized for direct access to the heart. In essence, there are a multitude of routine procedures in use for accessing the heart. Implantion of the claimed preparation is clearly within the skill in the art.

Even though each individual patient may be different in, for example, the size of the myocardial site to be treated, the accessibility of the site, and the age and stamina, a skilled artisan, such as an attending physician can easily determine an appropriate amount and duration of treatment in view of the scope of the claims and the teachings of the instant specification, which is accomplished using no more than routine procedures commonly practiced in the field.

The Office Action also contends that "the specification does not teach the potential effects or morphogens on any kind of cells in any kind of biological activities." Applicants are unable to discern how this rejection is applied in relation to the claims under examination. Clarification is respectfully requested. If this rejection is meant that the effect of administering morphogens to a mammalian subject may have unpredictable side effects, Applicants submit that the instant specification teaches on page 43, 1st full paragraph that "[i]t should be noted that no obvious morphogen induced pathological lesions arise when mature morphogen (e.g., OP-1, 20 mg) is administered daily to normal growing rats for 21 consecutive days. Moreover, 10 mg systemic injections of morphogen (e.g., OP-1) injected daily for 10 days into normal newborn mice does not produce any gross abnormalities."

The Office Action also contends that the specification does not teach isolating myogenic precursor cells and culturing said cells with a morphogen to produce proliferation or differentiation of said myogenic precursor cells into a functional myocardium.

Applicants submit that pages 13-16 of the specification explicitly teach in detail, under separate subsections 1, 2, and 3, isolating myogenic precursor cells from skeletal muscle, embryo, and established cell lines, respectively. The subsequent subsection 4 on pages 16-18 describes in detail how to culture these cells. Especially in page 18, the specification teaches treatment of these cells with morphogens. The Office Action also admits on page 3 of paper number 17 that "[t]he specification does teach the proliferation or differentiation of myogenic precursor cells into myocardium after morphogen treatment."

The Office Action also contends that the specification fails to provide any evidence that myogenic precursor cells have differentiated into functional myocardium. As discussed below, the teachings of the specification clearly show that myogenic precursor cells will differentiate into functional myocardium. Moreover, as also shown below, subsequent publications plainly refute the Examiner's position.

Applicants disclose, on page 12, lines 10-14, that "[t]he present invention depends, in part, upon the surprising discovery that morphogenically-treated mammalian myogenic precursors cells, when implanted in vivo at a site of lost or damaged mammalian myocardium, undergo a process of proliferation and/or differentiation to produce new and functional mammalian myocardium, thereby restoring or regenerating the lost or damaged tissue in whole or in part." (emphasis original) Thus, although the data is not shown, Applicants clearly indicate that an *in vivo* experiment had been performed to support the claimed invention. In fact, it is this unexpected *in vivo* experiment that eventually lead to the claimed invention.

Applicants hereby submit **Exhibit A** (Behfar *et al.*, *FASEB J.* **16**: 1558-1566, October, 2002), which provides *in vitro* and *in vivo* data which supports the claimed invention. Specifically, Behfar indicates in the abstract that "[i]n an environment of postmitotic cardiomyocytes, stem cells ... differentiated into ... ventricular myocytes beating in synchrony with host cells, a process significantly enhanced by TGF-beta or BMP2... In fact, only host cells that secrete a TGF-beta family member induced a cardiac phenotype in stem cells. *In vivo*, transplantation of stem cells into heart also resulted in cardiac differentiation provided that TGF-beta/BMP2 signaling was intact" (emphasis added). In fact, the article has also tested the more clinically relevant rescue of myocardium infarction: "[i]n infarcted myocardium, grafted stem cells differentiated into functional cardiomyocytes integrated with surrounding tissue, improving contractile performance." Thus, in this correlating *in vivo* model, myocardium precursor cells indeed differentiate into functional myocardium under the mandatory influence of the subject morphogen, as claimed in the instant application.

Applicants further submit **Exhibit B** (Orlic *et al.*, *Nature* **410**: 701-705, April 5, 2001), which demonstrates that bone marrow cells can also differentiate into functional myocardium *in vivo* when directly injected to infarcted myocardium (see, for example, abstract, Figures 1 & 6).

Exhibit C (Jackson et al., *J. Clinical Investigation* **107**: 1395-1402, June, 2001) additionally demonstrate that "side-population" cells, an adult hematopoietic stem cell capable of regenerating skeletal muscle, can also generate functional myocardium *in vivo* (see, for example, abstract, and towards the bottom of the right column of page 1395). All these working examples provide convincing post-filing evidence that myogenic precursor cells can differentiate into functional myocardium as claimed.

Finally, it is respectfully submitted that a working example is not required for filing. Pursuant to MPEP 2164.02, "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.'...An applicant need not have actually reduced the invention to practice prior to filing. Indeed, the fact of applicants' discovery and claimed invention is plainly evidenced by Behfar *et al.*, supra.

Applicants respectfully note that the Federal Circuit recently articulated a standard whereby the PTO must establish a rational connection between the agency's fact-findings and its ultimate action. *Dickinson v. Zurko*, 119 S.Ct. 1816 (1999). In light of Applicants' arguments of record, the substantial documentation that has been provided, and the presumption in favor of Applicants, it is respectfully asserted that the present rejection is not supported by substantial evidence, and as such, fails to rise above the "arbitrary, capricious" standard applied under the "substantial evidence" test of Section 706(2)(E) of the Administrative Procedure Act. The Examiner has not cited any relevant art nor relied on any other fact-finding results to rebut the presumption in favor of Applicants. If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

The Office Action also alleges that the specification fails to disclose that assays were employed to discern heart muscles (functional myocardium) from skeletal muscles. Relating to this, the Office Action also contends that the specification does not teach that a skeletal progenitor cell can switch fate after being in contact with morphogen and become a heart muscle cell useful for repairing heart tissues.

As an initial matter, it is important to note that the claims are directed, *inter alia*, to a "preparation of myogenic precursor cells" which, by definition, are myogenic precursors. The assay question raised in the Office Action is irrelevant to the *claimed* invention. As stated above, Behfar *et al.*, supra, demonstrate the fact of the claimed invention. This is all true notwithstanding the fact that the specification teaches on page 12 that "[i]n addition, the present invention depends, in part, upon the surprising discovery that non-myocardial cells, such as those obtained from mammalian skeletal muscle or embryonic myogenic precursor cells, may be induced to proliferate and differentiate into myocardium in a morphogenically permissive environment." The Office Action fails to provide any reasoning or scientific argument that would cast doubt on the stated result and the claimed subject matter. Thus, the Office Action fails to rebut the presumption in favor of the Applicants (see *Zurko* above). If the Examiner is relying on personal knowledge, Applicants respectfully request that the Examiner provide an affidavit pursuant to 37 C.F.R. 1.104(d)(2).

In addition, for a skilled artisan to practice the claimed invention, it is unnecessary to determine if the precursor cells have actually turned into heart muscle, since the specification itself teaches this. Even if such a verification step is optionally performed by a skilled artisan, the specification further teaches that the proliferation and/or differentiation of myogenic precursor cells into functional myocardium can be determined by assaying for their expression of "markers of a myocardial tissue phenotype" (page 33, line 6). As a skilled artisan would readily appreciate, such markers of myocardial tissue (as opposed to skeletal tissue) were well-known in the art at the time of filing of the instant application. For example, cardiac troponin I is a heart muscle-specific marker not found in skeletal muscles. The gene for this protein was cloned in 1990 (see Vallins *et al.*, *FEBS Lett* **270**(1-2): 57-61, September 17, 1990). Likewise, Townsend *et al.* (*Genomics* 21(2):311-6, May 15, 1994) cloned human cardiac troponin T, another heart muscle-specific marker in 1994. Antibodies against these markers are widely used in myocardial infarction diagnosis. In addition, Fields (WO 95/1079, cited in Paper No. 12) discloses on page 18 that the anti-MY-32 antibody can be used to differentiate skeletal vs. cardiac muscle; and on page 20 that isoforms 1, 2, and 3 of the LDH enzyme are cardiac muscle-specific, while isoform 5 is skeletal muscle-specific. And it was well-known in the art that differentiated cardiac muscle cells exhibit characteristic rhythmic beating in culture, another obvious phenotype for cardiac differentiation.

The Office Action also asserts that the specification does not teach therapeutic compositions for promoting the repair or regeneration of mammalian myocardium.

Applicants submit that the specification describes in detail the morphogens that can be used for the claimed invention (see, for example, pages 19-31), their production by various cells (see, for example, page 29, 1st full paragraph), methods of making soluble morphogens, a preferred form of morphogen for use in the claimed invention (see examples), and methods of formulating these morphogen proteins as pharmaceutical compositions for various routes of administration (see, for example, pages 39-44).

The Office Action also states that "there are no assays that teach how morphogens can used [sic] to treat damage [sic] myocardium."

Applicants submit that the specification specifically teaches how to make the subject morphogens and formulate them into pharmaceutical compositions suitable for use in the claimed invention (see above). The specification also discloses in detail how to use these compositions or morphogens to treat implanted or cultured myocardial precursor cells and how to isolate, culture, and implant myocardial precursor cells. Thus, there is no need for any kind of "assay" to teach how morphogens can be used to treat damaged myocardium.

The Office Action also asserts that it is unclear as to how to treat myogenic precursor cells with a morphogen subsequent to implanting said preparation of myogenic precursor cells into said mammal.

Applicants submit that the specification teaches at page 39, lines 21-28 that morphogens "may be provided to myogenic precursor cells by any suitable means, preferably directly (e.g., *in vitro* or locally after implantation, as by addition to culture medium, injection or topical administration to a tissue locus) or systemically (e.g., parenterally or orally). Preferably, the morphogen, morphogen inducer, agonist of a morphogen receptor, or small molecule morphogenic activator comprises part of an aqueous, physiologically acceptable solution so that in addition to delivery of the desired agent to the target cells, the solution does not otherwise adversely affect the cells' or subject's electrolyte and/or volume balance." Thus, the specification explicitly teaches how to treat these precursor cells subsequent to implanting precursor cells.

The Office Action further asserts that the specification states that it has not been shown that treatment of myogenic precursor cells with morphogen is useful in promoting the proliferation and/or differentiation of myogenic precursor cells into new and functional myocardium in a morphogenically permissive environment (page 5, line 3-10).

Applicants submit that the recited passage reads, "...it has never previously been shown or suggested that treatment of myogenic precursor cells with the morphogens, morphogen inducers, agonists of morphogen receptors, or small molecule morphogenic activators is useful in promoting the proliferation and/or differentiation of myogenic precursor cells into new and functional myocardium in a morphogenically permissive environment. Nor has it previously been shown or suggested that morphogenically-treated myogenic precursor cells are useful in the treatment of lost or damaged mammalian myocardium." (emphasis added) Thus, the recited section of the specification is discussing the state of the art prior to the filing of the instant application. Such statements offer nothing against the novelty and non-obviousness of the claimed invention. As stated above, the fact of applicants' invention has been duplicated by others. See, Behfar *et al.*, supra.

Finally, the Office Action states that the specification fails to disclose any examples demonstrating enablement of the recited claims.

As argued above, working examples are not required for filing, but are merely a factor in considering enablement. Furthermore, Applicants have stated that *in vivo* experiments fully support claims that reasonably correlate with the full scope of the claimed invention. See also, Behfar *et al.*, supra.

In summary, Applicants submit that the instant specification teaches in detail all necessary information for a skilled artisan to make and use the claimed invention, with no need to resort to any undue experimentation. Thus all pending claims fully comply with the enablement requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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Yu Lu, Ph.D.
Reg. No. 50,306

Customer No: 28120
Docketing Specialist
Ropes & Gray
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050